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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/621,725	03/21/96	LEHMANN	CASE-02138

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EXAMINER

SCHWADRON, R

ART UNIT PAPER NUMBER

1816

DATE MAILED 10/15/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/25/97

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-3, 18, 19 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-3, 18, 19 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413

_____'s Patent Drawing Review, PTO-948

_____, PTO-152

OFFICE ACTION ON THE FOLLOWING PAGES--

15. Claims 1-3,18,19 are under consideration. Claim 9 has been cancelled. Claims 18 and 19 are newly added.

RESPONSE TO APPLICANTS ARGUMENTS

16. Claims 1-3,18,19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

The specification does not disclose how to use the method of the instant invention for the treatment of autoimmune disease in vivo in humans. The method of the instant invention reads on a method for the treatment of human disease in vivo. Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification because the use for the instant invention disclosed in the specification is the in vivo treatment of disease in humans. The state of the art is such that is unpredictable from the mouse data disclosed in the specification as to how the instant invention could be used for the treatment of disease in vivo in humans. The specification provides no working examples indicating that the method of the instant invention can be used for the treatment of human disease. Regarding the in vivo EAE mouse data disclosed in the specification. Osband et al. teaches that there exists a lack of useful animal models that can be applied to immunotherapy. Osband et al. further teach that animal models are not generally predictive of therapeutic efficacy in humans as relates to immunotherapy regimens. (see page 193 in particular). Furthermore, EAE is not a naturally occurring disease, it is created by injecting certain strains of mice with xenogeneic MBP.

The use of any particular pharmaceutical therapy for the treatment of human disease is unpredictable in the absence of appropriate evidence demonstrating that said therapy can be used for the treatment of disease for the following reasons; (1) the protein may be inactivated before

producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Regarding applicants comments on pages 3-6 of the amendment filed 6/25/97, the following comments are made. Regarding applicants various comments about utility and the utility guidelines in page 5 of the instant amendment, applicant is reminded that the Official Gazette (1177 OG 146) states in column 1, third paragraph (under section I) that lack of a rejection under 35 U.S.C. §101 does not mean that a specification is therefore enabled under 35 U.S.C. §112, first paragraph. The claims of the instant invention read on a method for the treatment of human disease in vivo. Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method for human therapy. The state of the art is such that is unpredictable from the in vitro or in vivo mouse data disclosed in the specification as to whether (and how) the instant invention could be used for the treatment of disease in vivo in humans. Regarding the issue of whether the claimed invention can be used for the treatment of autoimmune disease per se, the art recognizes that not all autoimmune target antigens can be used in the claimed method. Cohen et al. (US Patent 5,578,3030) teach that administration of hsp65 (an autoimmune target antigen, see Abstract) in IFA results in the induction of disease in treated mice (see Example 9). Therefore, use of hsp65 in the claimed method would result in the induction of disease, not the treatment of disease. The only animal data disclosed in the specification involves the use of MBP or PLP for the treatment of EAE in rodents. There is no evidence of record that any other autoimmune antigen can be used for the treatment of any other autoimmune disease. Cohen et al. teaches that it is unclear as to what autoimmune antigens can be used for the treatment of any particular disease, wherein said antigen is administered with IFA. Thus, it is unclear as to whether any autoimmune disease per se can be treated with the claimed method because there is no murine data that addresses this issue, other than the specific example of murine EAE treated with MBP or EAE. There is no guidance in the

specification as to how to determine what autoimmune antigens can or cannot be used in the claimed method for the treatment of any particular autoimmune disease other than EAE in rodents. Regarding applicants comments about the mouse EAE model disclosed in the specification and the issue of whether said model is predictive as to whether the claimed method could be used for the treatment of human disease, Tisch et al. teach that it is unclear whether the EAE model is a suitable model for human MS. Regarding this issue Tisch et al. teach that:

“In this study and others it is apparent that peptide/antigen-specific immunotherapy, when applied to a highly defined model of autoimmunity, can be effective. However, could this approach be feasible in prevention or treatment of spontaneous autoimmune diseases such as MS, IDDM , or RA, in which the target autoantigen(s) is not known and a number of autoantigens appear to be involved in the disease process?”(page 437, middle column). Tisch et al. point out that models like EAE involve the treatment of rodents wherein the disease has not yet been induced (eg. the rodents receive treatment before the disease occurs, as per the model disclosed in the specification), while the treatment of human disease such as MS involves the treatment of already established disease (see page 437, middle column, last paragraph, continued on column 3). In fact, regarding the treatment of already established disease such as MS with the claimed invention, Tisch et al. teach that, “It is possible, however, that administering an antigen/peptide after pathogenic T cells have been activated may have an immunizing effect and exacerbate the disease condition.”(page 437, third column). Thus, Tisch et al. establish that it is unclear whether rodent EAE is actually a suitable model for human MS and that it is unclear whether the rodent data disclosed in the specification is predictive of whether the claimed invention can be used for the treatment of human disease.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tobin et al. (US Patent 5,674,978).

The claim is drawn to the method of claim 1. Tobin et al. teach that NOD mice were immunized with GAD in IFA and that said treatment could be used to treat IDDM in NOD mice (SEE columns 41 and 42). GAD is an autoimmune target antigen (see columns 1 and 2). Tobin et al. teach that GAD can be used to treat GAD associated autoimmune disease. Tobin et al. teach that the peptide can be injected along with a variety of different agents (see column 14, penultimate paragraph. Tobin et al. do not specifically teach immunizing humans with GAD in IFA. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Tobin et al. teach that NOD mice were immunized with GAD in IFA and that said treatment could be used to treat IDDM in NOD mice, that GAD can be used to treat GAD associated autoimmune disease in humans and that the peptide can be injected along with a variety of different agents (see column 14, penultimate paragraph). One of ordinary skill in the art would have been motivated to do so because IFA is encompassed by the various agents disclosed by Tobin et al. in column 14, penultimate paragraph, as injectable along with GAD.

19. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tobin et al. (US Patent 5,674,978) as applied to claim 1 above, and further in view of Namikawa et al. and prior art disclosed in the specification.

The claim is drawn to the method of claim 3. The previous paragraph makes obvious the claimed invention except for the use of MBP to treat MS. Namikawa et al. teach that immunization with MBP in IFA prevents EAE in rats (see page 932, first column, first paragraph). The specification discloses that the art recognizes certain similarities between EAE and human MS (see page 2, first paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed method because the previous paragraph makes obvious the claimed invention wherein an autoimmune antigen is administered in IFA to treat an autoimmune disease in humans, while Namikawa et al. teach that immunization with MBP in IFA prevents EAE in rats and the art recognized similarities between EAE and human MS. One of ordinary skill in the art would have been motivated to do the aforementioned because Tobin et al. teach treatment with autoimmune antigens for the treatment of human disease.

Regarding applicants comments on page 7 of the instant amendment as they apply to this

new rejection, Namikawa et al. teach that, "Furthermore, immunization of rats by injection of BP in IFA not only prevents subsequent active or passive induction of EAE, but also has been reported to induce cells capable of preventing active sensitization of recipients." (page 932, first column, first paragraph). Regarding applicants comments about the safety and efficacy of said treatment, virtually no known pharmaceutical agent currently used in humans is without side effects or is known to possess efficacy in every treated individual.


20. Claims 1-3,18,19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tobin et al. (US Patent 5,674,978) in view of Namikawa et al. and prior art disclosed in the specification as applied to claims 1 and 3 above, and further in view of Goodwin et al. (US Patent 5,569,585).

The claims are drawn to the method of claims 2,18,19. The previous paragraph makes obvious the claimed invention except for the use of the immunoassay recited in the claims. Namikawa et al. teach that after immunization, the response of cells to a T cell mitogen is tested (see Table 3 and page 934, column 1). The response of T cells would have been alternatively measured using art known lymphokine assays, because the art recognizes that activated T cells produce lymphokines in response to antigenic stimulation (see Goodwin et al., see column 10, penultimate paragraph). ELISA assays for T cell cytokines are known in the art as is the membrane recited in claim 2 (see specification, page 8, first paragraph and Goodwin et al., column 10). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the previous rejection makes obvious the claimed invention except for the use of the immunoassay recited in the claims, while Namikawa et al. teach that after immunization, the response of cells to a T cell mitogen is tested and the response of T cells would have been alternatively measured using art known lymphokine assays, because the art recognizes that activated T cells produce lymphokines in response to antigenic stimulation (see Goodwin et al., see column 10, penultimate paragraph) and ELISA assays for T cell cytokines are known in the art. One of ordinary skill in the art would have been motivated to do the aforementioned because Namikawa et al. teach that after immunization, the response of cells to a T cell mitogen is tested and the response of T cells would have been alternatively measured using art known lymphokine assays, because the art recognizes that activated T cells produce lymphokines in response to antigenic stimulation.

21. No claim is allowed.

22. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-3014.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00. The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.



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PRIMARY EXAMINER
GROUP 1800

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Art Unit 1816
October 10, 1997